SCIENTIFIC LETTERS

Altered CD18 leucocyte integrin expression and adhesive function in patients with an acute coronary syndrome

The adhesion of leucocytes to vascular endothelium is fundamental to the pathogenesis of atherosclerosis and the acute coronary syndromes. The CD11b/CD18 receptor is particularly important in this process. This molecule is expressed on both neutrophils and monocytes. In common with other integrin receptors it consists of α and β subunits (CD11b and CD18, respectively), which allow binding of leucocytes to the endothelial surface.[1]

The aims of our study were: (1) to compare the expression of CD11b and CD18 on peripheral neutrophils and monocytes in patients with an acute coronary syndrome, patients with stable coronary artery disease, and healthy controls; and (2) to assess any functional change in neutrophil adhesion in the acute coronary syndrome.

Twenty two consecutive patients with an acute coronary syndrome were studied. None had received thrombolytics or glycoprotein IIb/IIIa inhibitors and none had undergone coronary revascularisation. All were on maintenance aspirin (n = 19) or had received > 12 hours of such treatment in hospital (n = 3). Twelve patients with stable coronary artery disease were also studied. All had a > 50% stenosis of at least one major coronary artery, had stable cardiac symptoms over the past six months, and were taking maintenance aspirin. The third group consisted of 12 healthy volunteers with no cardiac history or symptoms. These subjects were asked to take aspirin for three days before blood sampling. None of the patients or volunteers studied had conditions known to affect leucocyte adhesion molecule expression or function.

Cell surface expression of the CD11b and CD18 subunits was determined by flow cytometry. Functional changes in neutrophil adherence were assessed using a well validated technique that relies on their ability to adhere to nylon columns.[2] The assay determines percentage neutrophil adherence, with 98% of this adhesion mediated by CD18.[2] In our laboratory it has a coefficient of variation of 5.4%.

Results are presented as mean (SE) unless otherwise stated. Kruskal-Wallis and Mann-Whitney *U* tests were used to compare groups, with a double sided p value < 0.05 considered significant.

Among the 22 patients with an acute coronary syndrome the mean duration of symptoms before blood sampling was 15.4 (2.2, range 1–36) hours. Fourteen patients were ultimately diagnosed as having unstable angina, five had a non-Q wave myocardial infarction, and three sustained a Q wave myocardial infarction.

Expression of CD11b and CD18 was similar on neutrophils and monocytes from patients with stable coronary artery disease and healthy controls (table 1). However, monocytes from patients with an acute coronary syndrome had higher expression of CD11b and CD18. Neutrophil CD18 expression was also higher in unstable patients, when compared with healthy controls, though not those with stable coronary artery disease (table 1). There was no difference in CD18 mediated neutrophil adhesion in healthy subjects and patients with stable coronary artery disease (table 1). In contrast, CD18 mediated neutrophil adhesion was lower among patients with an acute coronary syndrome than either of these control populations. Neutrophil adhesion was lowest among patients with an acute coronary syndrome who had evidence of myocardial damage at the time of blood sampling (concurrent cTnI concentrations > 0.1 ng/ml). Conversely, the expression of CD11b and CD18 was highest among patients with positive cTnI. The numbers in these subgroups are, however, small.

Patients with an acute coronary syndrome in whom cTnI is negative lie between those with stable symptoms (who have lower CD11b and CD18 expression but greater CD18 mediated neutrophil adhesion) and patients with positive cTnI (who have higher cell surface expression of CD11b and CD18 but reduced function). This trend is particularly pronounced in the case of CD11b expression by monocytes (p < 0.01), and to a lesser extent for CD18 mediated neutrophil adhesion (p = 0.06) and expression of this molecule by monocytes (p = 0.07).

This small study provides further evidence that unstable coronary artery disease is associated with an inflammatory response. In particular, it demonstrates changes in peripheral leucocyte adhesion molecule expression and, perhaps more importantly, function among patients with an acute coronary syndrome. The principal differences are in the expression of the CD11b and CD18 on monocytes. Both of these molecules are more strongly expressed among patients with unstable disease. Neutrophils from patients with acute coronary syndrome also express more CD18 than those from healthy controls. Despite this, CD18 mediated neutrophil adherence is lowest among patients with an acute coronary syndrome. The increases in monocyte CD11b/CD18 expression and reductions in neutrophil CD18 function are most pronounced in patients with concurrent evidence of myocardial necrosis, though less prominent changes are also evident in patients without evidence of cardiac damage.

Increased expression of CD11b/CD18 is found on neutrophils and monocytes sampled from the coronary sinus blood of patients with unstable angina and in peripheral blood following acute myocardial infarction.[3 4] It has been suggested that these latter increases are related to myocardial necrosis.[4] While this may accentuate leucocyte activation, the current data suggest that particularly monocyte induction is apparent even in the absence of cardiac damage. Activation of monocytes may result in increased adherence to endothelial surfaces and transmigration into the subendothelium, where they can further destabilise atherosclerotic plaques. Monocyte infiltration may also cause increased concentrations of tissue factor, enhancing the risk of thrombotic vessel occlusion and local vasoconstriction.

Intuitively, the reduction in CD18 mediated neutrophil adhesion in patients with an acute coronary syndrome is unexpected, particularly when increased cell surface expression of CD18 is apparent. Similar reductions in neutrophil adherence have, however, been demonstrated in acute sepsis, and increased CD18 integrin expression is not always associated with altered function. Perhaps the most likely explanation is that increases in CD18 mediated adhesion are transient. Certainly, this appears to be the case in vitro, where phorbol esters induce a 10-fold increase in CD11b/CD18 adherence within 15 minutes, falling to below normal within an hour.[5] This is associated with a much smaller increase in cell surface CD11b/CD18 expression (2–3 times) which continues to rise steadily beyond this time point.[5]

In addition to the small sample size, the current study has several limitations. Aspirin reduces the adherence of neutrophils and lymphocytes, and we therefore controlled for such treatment. It is, however, uncertain what influence other agents might have on CD18 expression and function. Similarly, patients with an acute coronary syndrome had a higher prevalence of cardiovascular risk factors and this could represent an alternative explanation for our findings.

In conclusion, the current study reports increased CD11b/CD18 expression on leucocytes from patients with an acute coronary syndrome. This is associated with reduced CD18 mediated neutrophil adhesion in vitro. Further work is required to clarify the reasons for this paradox and to assess whether the observed changes in leucocyte CD18 biology represent a cause or an effect of the acute event.

Table 1 CD18 and CD11b expression on leucocytes plus percentage neutrophil adhesion in patients with an acute coronary syndrome (with and without concurrent cardiac troponin I concentrations > 0.1 ng/ml), patients with stable coronary artery disease, and healthy controls

	Neutrophils		*Monocytes*		*% Neutrophil adhesion*
	CD11b	*CD18*	*CD11b*	*CD18*	
Acute coronary syndromes (n=22)	4.02 (0.45)	1.89 (0.19)*	5.74 (0.57)*	4.92 (0.41)†	9.5 (2.1)
Positive cTnI (n=10)	4.34 (0.73)	2.01 (0.29)	6.45 (0.80)	5.17 (0.62)	8.7 (3.4)
Negative cTnI (n=12)	3.76 (0.58)	1.79 (0.26)	5.15 (0.80)	4.71 (0.57)	10.3 (2.6)
Stable coronary artery disease (n=12)	2.83 (0.32)	1.64 (0.17)	3.33 (0.27)‡	3.72 (0.27)§	15.3 (2.1)§
Healthy controls (n=12)	3.43 (0.32)	1.20 (0.15)	3.77 (0.27)	3.08 (0.25)	15.5 (2.5)§

Results expressed as mean (SEM) fluorescence intensity.
*p < 0.05 *v* healthy controls; †p < 0.01 *v* healthy controls; ‡p < 0.01 *v* acute coronary syndrome; §p < 0.05 *v* acute coronary syndrome.

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Progressive ECG changes before the onset of atrial flutter in adult congenital heart disease patients

Atrial flutter is a frequent complication in patients with adult congenital heart disease either during natural history or after surgical repair.[1 2] The incidence of such an arrhythmia increases postoperatively with time and is usually associated with complex atrial surgery.[3 4] When it occurs, atrial flutter compromises haemodynamics, reduces exercise tolerance, and is often resistant to medical treatment. The P wave has been found to change its electrical characteristics before atrial fibrillation supervenes in patients with coronary artery disease.[5] We sought to study the same hypothesis in 39 adult congenital heart disease patients, 31% of them with Mustard or Fontan surgery, who developed atrial flutter long after surgical repair, and compare them with 30 diagnosis matched controls who had never developed atrial arrhythmias. All the patients studied had undergone at least three consecutive annual ECG recordings before the onset of flutter, which were compared with those recorded similarly over three years in controls. P wave amplitude and duration were measured using an electronic "digimetric" caliper (Mitutoga) and a magnifier to confirm reproducibility.

In the control group there was no change in P wave duration or voltage over the three year study period. Although there was no difference in P wave duration in the first ECG recording between patients and controls, in those who subsequently developed flutter, it was significantly longer in the second (115 (24) ms *v* 104 (16) ms, $p < 0.01$) and the third (126 (24) ms *v* 106 (15) ms, $p < 0.001$) recordings before the onset of flutter. In the patient group, P wave duration increased by 11 ms annually for the two years before development of flutter. Thirty five of 39 (90%) patients had a P wave duration over 120 ms on the third ECG compared to 10/30 (33%) controls; this difference in incidence was significant ($p < 0.001$). P wave voltage was significantly higher in patients on the first ECG compared to the controls (1.9 (0.9) mV *v* 1.5 (0.5) mV, $p < 0.05$), but was not different in the second or the third recordings.

Patients with complex congenital heart disease often require multiple atrial reparative surgery. Even those who do not need such corrective surgery early in life are known to develop significant degree of tricuspid regurgitation over the years. A number of possible mechanisms can thus contribute to the occurrence of flutter in these patients. Atrial disease resulting from multiple sutures, chronic tricuspid valve regurgitation, or atrial remodelling may all constitute the substrate for flutter.[6–8] Progressive ventricular disease, and increasing end diastolic pressure, may result in increased atrial volume and pressure, and hence atrial myocardial stretch is similar to the ventricle when it becomes arrhythmogenic. These mechanisms have been proposed in patients with complex surgical repair particularly after Mustard and Fontan operations. Regardless of the underlying anomaly, and possible mechanism, it seems that progressive broadening of P wave duration and a fall in its voltage commonly precede the occurrence of flutter in such patients, in a fashion similar to that of the QRS duration in patients with dilated cardiomyopathy. Since atrial flutter in adult congenital heart disease is clinically deleterious and may eventually resist medical or electrical cardioversion, identifying P wave disturbances during follow up in these patients may alter their conventional management policy and raise the possibility that this significant complication may be delayed or prevented.

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Dissolution of tungsten coils leads to device failure after transcatheter embolisation of pathologic vessels

Coil embolisation has been the standard transcatheter technique for occlusion of pathologic vessels, aneurysms, and fistulae for more than three decades. Tungsten is an attractive material for use as an endovascular coil, because of its high radiopacity and thrombogenicity.[1] Recently, decreasing radiopacity has been reported in patients after implantation of tungsten coils (MDS, Balt

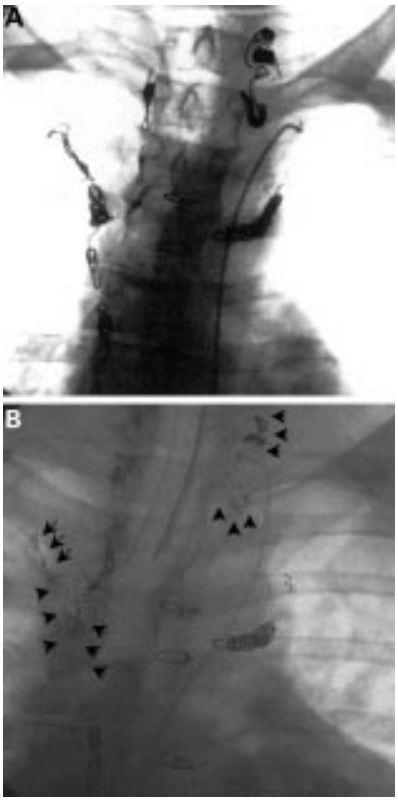

Figure 1 (A) Fluoroscopy immediately after implantation of tungsten coils in a 22 year old patient with multiple aortopulmonary collaterals. (B) Fluoroscopy six months after implantation. Decreased radiopacity of the tungsten coils (arrows).

Extrusion, Montmorency, France) into cerebral aneurysms > 30 months after implantation.[2] Analysis of the coils in an experimental study demonstrated "a clear degree of iron" around the MDS coil occluded arterial aneurysms. The authors concluded: (1) that the coils are not purely tungsten; (2) that there was corrosion of the coils; and (3) that it may be dangerous to use this type of coil in patients.[3] To assess whether similar findings could be observed in our patients all transcatheter tungsten coil implantations performed at our institution were reviewed. Furthermore a detailed analysis of the composition of the MDS coil was performed. Out of 104 patients with transcatheter coil occlusion of pathologic vascular connections 87 tungsten coils were implanted in 21 patients. Angiography after the implantation confirmed complete coil occlusion of the vessel in all patients.

Serum tungsten concentrations were analysed by inductive coupled plasma mass spectrometry focusing on the isotope 184 (Labor Schiwara, Hafer Sende, Bremen, Germany); normal values were used from a large cohort study[4]. The MDS coils were analysed using both inductively coupled plasma atomic emission spectroscopy (ICP-MS; VG Elemental PlasmaQuad II Turbo+) and inductively coupled plasma atomic emission spectroscopy (ICP-AES; Spectro-Flame-EOP) after pressure dissolution of the coil with HF, HNO_3, H_2O_2, $HClO_4$ at 37–200°C and by use of wavelength dispersive *x* ray spectrometry (WDS). To avoid interference with surface contaminants, the coils were embedded in a conductive embedding medium and ground to achieve representative cross sections.

In 21 patients who received tungsten coils a mean follow up of 97 months (two days to 38 years) was achieved. Fluoroscopy performed in 14/21 patients revealed a decreased radiopacity in 9/14 patients (fig 1). Repeat angiography performed in 7/21 patients demonstrated recanalisation of 1–4 of the previously MDS occluded vessels in 5/7 patients; in all patients with recanalised vessels a decreased radiopacity of the coils was observed. Serum concentrations for tungsten were greatly increased in 8/8 patients, ranging from 2.0 µg/l to 14.4 µg/l (mean 6.43 µg/l, normal value < 0.2 µg/l). No unexplained clinical symptoms were reported on follow up examination. The MDS coils we examined are produced from > 99.9 mas.% tungsten.

Dissolution and device failure of a "permanent" medical implant caused by recanalisation of a previously occluded vessel can occur along with raised serum concentrations of the degradation products. It may be speculated that minimal residual shunting was present in our patients early after coil implantation, thereby accelerating the degradation of tungsten by keeping the pH at a level ≥ 7.4. However, no adverse clinical effects were identified during follow up of the patients. Although there are no reports published on toxicity or unexplained clinical symptoms in patients receiving tungsten coils, there is a lack of concise data on the toxicity and clearance of tungsten in humans.[5] Our own analysis shows that MDS coils are produced from pure tungsten (> 99.9 mas.%). We assume that the analysis performed by others[3] was undertaken with an energy dispersive *x* ray spectrometer (EDX) and the deviation may be caused by incidental superposition of the energy of ultimate and subordinate lines; adequate results can only be obtained with a wavelength dispersive spectrometer because of its superior specificity.

We conclude that tungsten coils can dissolve leading to implant failure and greatly increased serum tungsten concentrations. The clinical use of these coils can no longer be recommended. Although there is lack of evidence for in vitro or in vivo toxicity of tungsten, patients with MDS coils should be followed thoroughly with tests for serum tungsten concentrations, and liver and renal function. Repeat angiography may be warranted if decreased radiopacity is observed.

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